R
856
N287
1980

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH

DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT FY 1980

Dr. Murray Eden, Chief

R
.S5a
No 21
1920

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10001-12 BE

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Dedrick	Chief	ChES BEIB DRS
	J.M. Collins	Chemical Engineer	BEIB DRS
OTHER:	D.S. Zaharko	Pharmacologist	LCHPH NCI
	F. King	Associate Professor	Howard Univ.
	A.M. Guarino	Chief	LT NCI
	R.J. Lutz	Chemical Engineer	BEIB DRS
	M.W. Anderson	Mathematician	PB NIEHS
	P.M. Bungay	Chemical Engineer	BEIB DRS
	H.B. Matthews	Pharmacologist	NTP NIEHS
	I.G. Sipes	Assistant Professor	Univ. of Arizona
	C.E. Myers	Oncologist	CPB NCI
	J.L. Speyer	Oncologist	MB NCI
	M.F. Flessner	Chemical Engineer	US Coast Guard

COOPERATING UNITS (if any)

LCHPH-NCI; PB-NIEHS; AK-CU Program NIAMDD; M-NCI; NTP-NIEHS; CPB-NCI.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate data from animals to man and thereby improve chemotherapy, hemodialysis, and risk assessment.

PHS-6040
(Rev. 10-76)

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide a rational basis for extrapolating toxicity from animals to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimizing cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of *in vitro* thermodynamic and kinetic data to *in vivo* cases.

(5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on intraperitoneal drug administration.

Methods Employed: Mathematical models are developed from physicochemical, physiological, and anatomical information and the principles of chemical reaction engineering. Resulting sets of differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:

(1) A pharmacokinetic model developed to describe the distribution and disposition of polychlorinated biphenyls in the rat has been employed to analyze data from the dog and monkey. Estimates of tissue blood flow were used as intercompartment transport parameters for all tissues except skin; as had been observed in the rat, skin of the monkey and dog appeared to exhibit significant departure from flow limitation. Partition coefficients between several major tissues and blood are similar for 2,4,5,2 ,4 ,5 -hexachlorobiphenyl in rat, dog, and monkey. The intrinsic rates of metabolism of this compound and of the 4,4 congener (ml/min kg body weight) are highest in the dog and lowest in the monkey. The importance of position of the substituents is shown by the fact that the intrinsic rates of metabolism of 2,3,6,2 ,3 ,6 -hexachlorobiphenyl are more than an order of magnitude higher than those of the 2,4,5-isomer in both dog and monkey. Kidney clearances of lumped "metabolite" (per unit of body weight) are low, with the rat exhibiting somewhat higher values than the dog or monkey for the two congeners for which data exist in all species.

(2) An analysis was performed of the disposition of chlordecone (Kepone) in the rat. Particular attention was devoted to the role of the intestinal tract in excretion, as well as absorption, of this halogenated pesticide. The chlordecone disposition was quantitated by development of a mathematical model of the physiological pharmacokinetic type. The model includes a detailed description for the GI tract in which the organs of the GI tract are segmented into a series of well-mixed compartments representing stomach, small intestine, cecum, and large intestine. The model is applied to describing the movement of a nonabsorbable tracer along the GI tract in addition to the enteric transport of chlordecone. Values for the gut wall permeability-area products for chlordecone were determined for the rat and estimated for man based on scale-up considerations. The potential for enhancement of excretion rates from victims of poisoning by lipophilic chemicals through use of orally administered adsorbents was examined.

(3) A two-compartment physiologically-based pharmacokinetic model has been developed to describe the clinical pharmacokinetics of the anticancer drug 5-fluorouracil (5FU) following intravenous administration of a rapid bolus or continuous infusion. The principal feature of this model is its ability to explain the differences in clearance observed between these two schedules by the use of saturable whole body clearance. The model has also been extended to simulate intraperitoneal administration.

(4) Our understanding of intraperitoneal drug kinetics has been enhanced by a clinical study in which catheters were placed in the portal vein, hepatic vein, an artery and a peripheral vein. Samples were obtained from these sites and also from the peritoneal fluid during 5FU administration. Calculations of hepatic extraction and estimates of the fraction of drug absorbed via the portal system were made from this unique data set.

(5) The initial results obtained from adriamycin administration in the large volume intraperitoneal protocol have been in agreement with predictions - made from scale-up of rat experiments and modifications of systemic pharmacokinetic models. Distributed models of peritoneal uptake are currently being explored.

(6) A physiologic pharmacokinetic model is being developed for 2'-deoxycoformycin (DCF) in the mouse. The major route of excretion of DCF is through the kidneys. Kidney clearance of DCF is nearly twice the estimated glomerular filtration rate indicating considerable tubular secretion. No metabolites of DCF have been found in the urine, but a small amount of a phosphorylated species forms intracellularly. DCF is a tightly bound inhibitor of the ubiquitous enzyme adenosine deaminase. The modeling process uses a sequential parameter estimation procedure. The parameters for the individual tissues are fitted using a hybrid model consisting of model equations for the specific tissue and a curve-fitted equation for the plasma data. The pharmacokinetics for the total animal are then determined by solving all equations simultaneously and predicting the plasma concentration from the mass balance.

Significance: Drugs and other chemicals are tested for effect in animals, with the aim of extrapolating results to man. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events and drug interactions. Continued clinical emphasis through support of intraperitoneal procedures and other measures to overcome drug resistance. Increased emphasis on research designed to investigate distribution and metabolism of environmental contaminants. Investigation of use of *in vitro* assays of chemical metabolism in conjunction with pharmacokinetic models for quantitative prediction of metabolism *in vivo*.

Publications:

Speyer, J.L., Collins, J.M., Dedrick, R.L., Brennan, M.F., Londer, H., DeVita, Jr., V.T., and Myers, C.E. Phase I and pharmacological studies of intraperitoneal (I.P.) 5-Fluorouracil (5-FU). Proc. 15th Ann. Mtg. Am. Soc. Clin. Oncology (Abstract) 20: 352, 1979.

Dedrick, R.L. Pharmacokinetics of Vinylidine Chloride (Letter). Environmental Health Perspectives 28: 311-313, 1979.

Bungay, P.M., Dedrick, R.L., and Matthews, H.B. Pharmacokinetics of Halogenated Hydrocarbons. Ann. N.Y. Acad. Sci. 320: 257-270, 1979.

Bungay, P.M., Dedrick, R.L., and Matthews, H.B. Pharmacokinetics of environmental contaminants in Dynamics, Exposure and Hazard Assessment of Toxic Chemicals in the Environment. R. Haque (Ed.), Ann Arbor Science Publishers, 1980, pp. 369-377.

Yang, K.H., Fung, W.P., Lutz, R.J., Dedrick, R.L., and Zaharko, D.S. In Vivo Transport of Methotrexate in Murine Lewis Lung Tumor. J. Pharm. Sci. 68: 941-945, 1979.

Dedrick, R.L., and Bischoff, K.B. Species similarities in pharmacokinetics. Fed. Proc. 39: 54-59, 1980.

Himmelstein, K.J. and Lutz, R.J. A Review of the Applications of Physiologically Based Pharmacokinetic Modeling. J. Pharmacokinetics and Biopharmaceutics, 7: 127-145, 1979.

Speyer, J.L., Collins, J.M., Dedrick, R.L., Brennan, M.F., Buckpitt, A.R., Londer, H., DeVita, V.T., Jr., and Myers, C.E.: Phase I and pharmacologic studies of 5-fluorouracil administered intraperitoneally. Cancer Research 40: 567-572, 1980.

Speyer, J.L., Sugarbaker, P.H., Collins, J.M., Dedrick, R.L., Klecker, R.W., Jr., DeVita, V.T., Jr., and Myers, C.E.: Portal uptake and hepatic metabolism of 5-fluorouracil (5-FU) administered by intraperitoneal (ip) dialysis (abstract). Proc. Am. Assoc. Cancer Research 21: 158, 1980.

Ozols, R.F., Young, R.C., Speyer, J.L., Weltz, M., Collins, J.M., Dedrick, R.L., and Myers, C.E.: Intraperitoneal (IP) adriamycin (ADR) in ovarian carcinoma (OC) (abstract). Proc. Am. Soc. Clin. Oncology 21: 425, 1980.

Collins, J.M., Dedrick, R.L., King, F.G., Speyer, J.L. and Myers, C.E.: Nonlinear pharmacokinetic models for 5-fluorouracil in man: intravenous and intraperitoneal routes. Clin. Pharmacol. Therap. 28: 235-246, 1980.

Collins, J.M. and Dedrick, R.L.: Pharmacokinetics of anticancer drugs. In Clinical Pharmacology of Antitumor Drugs, B.A. Chabner (Ed.), Saunders, Philadelphia (In press).

Lutz, R.J., Dedrick, R.L. and Zaharko, D.S.: Physiological pharmacokinetics: an *in vivo* approach to membrane transport. *J. Pharmacol. Therapeutics* (In press).

> Reprinted in International Encylopedia of Pharmacology and Therapeutics, Membrane Transport of Chemotherapeutic Agents, I.D. Goldman (Ed.), Pergamon, New York (In press).

King, F.G. and Dedrick, R.L.: Pharmacokinetic model for 2-amino-1,3,4-thiadiazole in mouse, dog, and monkey. *Cancer Treatment Rep. 63*: 1939-1947, 1979.

Speyer, J.L., Sugarbaker, P.H., Collins, J.M., Dedrick, R.L., et al.: Portal levels of hepatic clearance of 5-fluorouracil after intraperitoneal administration in man. *Cancer Research* (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10002-15 BE

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Boretos	Physical Scientist	BEIB DRS
OTHER:	C.L. McIntosh	Senior Surgeon	SU NHLBI
	W.S. Pierce	Associate Professor	Penn. State Univ.
	J. Doppman	Radiologist	DR CC

COOPERATING UNITS (if any)

SU-NHLBI; DR-CC; Pennsylvania State University

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of biomaterials used for specific implants with the physiological environment and to explore specially prepared materials and design features with respect to their suitability and performance in a variety of contexts. After removal from the host organism, implants will be examined for lipid absorption, calcium and/or protein deposition, changes in surface-free energy, and alteration of physical properties. Prostheses such as artificial hearts, heart valves and catheters will be employed. Observations should include scanning electron microscopy (SEM), infrared spectroscopy, contact angle measurements, and energy dispersive X-ray analysis. Physical measurements will be made of tensile properties, flexural-fatigue resistance, electrical properties, hardness, density, coefficient of static and kinetic friction, hydrophilicity, and other surface and bulk properties.

PHS-6040
(Rev. 10-76)

Objectives: Elucidate the interaction of polymers, metals, and ceramics used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic composition of the biomaterials is carefully controlled, and modifications are employed to enhance acceptability by the living system. After removal, implants are examined for lipid absorption, protein and/or calcium deposition, changes in surface-free energy, and alteration of physical properties. Observation techniques include SEM, infrared spectroscopy, contact angle measurements, energy dispersive X-ray analysis, and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied *in vitro* in a test apparatus. Electronic implants are examined periodically *in vivo* for changes in threshold levels, corrosion, and tissue reactivity. *In vitro* studies of the aforementioned are designed to accelerate fatigue testing and methods of improvement through heat treatment of the metal components undergoing stress. Surfaces of catheters are modified using surface treatments of grafted polymers and copolymers to reduce drag through the blood vessels. These catheters are tested for burst strength, stiffness, tensile strength, and density. The basic composition is modified through compounding. Embolizing agents consisting of composites of polymers, ceramics, and metals are being devised for delivery through the catheter systems so as to block arteries and vessels in the treatment of lesions such as aneurysms and arteriovenous malformations.

Major Findings: A number of forms and compositions of embolizing agents implanted in cats and monkeys have proven to be unsatisfactory due to localized tissue reactivity.

Tensile properties of selected polyurethanes can be significantly enhanced for implant use through a controlled annealing process.

Perfusion of drugs through micro-catheters can be determined through a calibrated capillary as a function of viscosity and pressure.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart-assist devices, vascular implants, indwelling catheters, and subcutaneous uses.

Proposed Course: Extend experimental studies to further characterize the surface and bulk properties of biomaterials and, more specifically, determine their interactions with blood and subcutaneous tissue to facilitate development of better surgical implants.

Publications:

Boretos, J.W.: Encapsulation considerations for acute/long term durability of electronic implants. In M. Szycher and W.I. Robinson (Eds.) Synthetic Biomedical Polymers: Concepts and Practice, Technomics, Inc., Westport, Conn. (In press).

Boretos, J.W.: Polymers for implantable telemetry devices. Proceedings of workshop on "Implantable Transducers and Systems: Packaging Methods and Testing Criteria." Stanford University, June 27-29, 1979.

Boretos, J.W.: The chemistry and biocompatibility of specific polyurethane systems for medical use. In D.F. Williams (Ed.) Biocompatibility of Clinical Implant Materials, CRC Press (In press).

Boretos, J.W.: Past, present and future role of polyurethanes for surgical implants. J. Pure and Applied Chemistry 52: 1851, 1980.

Boretos, J.W., Terek, R.M., Girton, M.E. and Doppman, J.L.: Cohesive and frictional reduction of intra-arterial micro-catheters. Proceedings of the 33rd Annual Conference on Engineering in Medicine and Biology, Washington, DC, Sept. 1980 (In press).

Boretos, J.W., Dengler, W.C., Terek, R.M., Edwards, K.J., Jr., Wilkins, J.F., Girton, M.E., and Doppman, J.L.: Integral balloon catheter for interventional radiology. Proceedings of the 33rd Annual Conference on Engineering in Medicine and Biology, Washington, DC, Sept., 1980 (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10007-06 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	B.A. Vern	Clinical Associate	CNB NINCDS
	W.C. Whitehouse	Electronics Technician	ADM CC
	N. Mutsuga	Visiting Fellow	CNB NINCDS

COOPERATING UNITS (if any)

CNB-NINCDS; AB-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c) NEITHER]

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Oxidative metabolism, as indicated by the fluorescence of nicotinamide adenine dinucleotide (NADH) and oxygen consumption, was assessed to investigate potassium ion kinetics in the cat brain. Research was conducted to determine if the potassium clearance process is active or passive after activation of the cortex. Investigations were also conducted to determine the applicability of the NADH fluorescence technique to exposed myocardium. Active work on this project was completed before September 30, 1977; two papers were published subsequently in 1979 listed last year and an additional paper this year.

Methods Employed: The NADH fluorescence at 470 nM is excited by illumination with ultraviolet light at 360 nM obtained from a high pressure Hg arc lamp. To compensate for blood volume changes within the field of interest, we developed and used a television fluorometer employing fluorescein dye as a reference. The technique, initially used for study of cat brain, was also applied successfully to exposed myocardium.

A potassium-sensitive microelectrode system was employed for measuring both extracellular and intravenous potassium ion levels.

Direct cortical oxygen consumption measurements were made by cannulation of the sagittal sinus and monitoring the flow rate and hemoglobin saturation of the blood flowing out of the sinus. The calculated oxygen consumption is proportional to the arterial-venous oxygen concentration difference multiplied by the flow rate.

For the Q_{10} experiments, the exposed cat hippocampus temperature was either elevated or lowered by use of a controlled temperature stream of artificial spinal fluid which flowed over the surface of the hippocampus. Surface temperature was monitored by a small thermistor probe.

Major Findings: The NADH dynamics observed in the myocardium are similar to those observed in the cortex.

Blood volume in transiently ischemic myocardial tissue may increase due to relaxed muscle tone.

Fluorescein fluorescence was found to be an excellent indicator of myocardial perfusion.

Agreement was found between an analytical model for potassium clearance and experimentally determined potassium kinetics. This agreement provided further evidence of the active clearance process previously suggested by Q_{10} measurements and the slowing of potassium clearance during periods of hypotension.

Publications:

Vern, B.A., Schuette, W.H., Mutsuga, N., and Whitehouse, W.C.: Effects of ischemia on the removal of extracellular potassium in cat cortex during pentylenetetrazol seizures. *Epilepsia*, 20: 711-724, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10011-06 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Electrical Safety Program for Clinical Center Patients and Patient Care and Treatment Areas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Corsey	Electronic Engineer	BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	C. Strong	Environ. Services Officer	CC
	T. Johnson	Administrative Officer	CC
	J. Bucolo	Electronic Technician	BEIB DRS
	W. Connoley	Super. Electronic Tech.	BEIB DRS

COOPERATING UNITS (if any)

ADM-CC; CCIS-BEIB

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL:	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The electrical safety program assures a hazard-free electrical environment for Clinical Center patients by testing clinical electrical equipment on a regular basis, investigating electrical shocks in patient areas, providing instruction to Clinical Center and Division of Safety personnel, assuming compliance with standards of the Joint Commission on Accreditation of Hospitals and the National Electric Code, participation in Clinical Center committees relating to medical equipment, inspecting new construction and renovation, design and modification to test equipment and participation in the formulation of national standards.

Objectives: To eliminate electrical shock hazards from Clinical Center patient areas; to assure Clinical Center compliance with requirements for accreditation; to participate in activities of the Clinical Center Safety Committee and the Medical Device Evaluation and Standardization Committee; to investigate electrical shocks and burns and recommend corrective action; to inspect new and renovated patient areas for proper grouding and electrical service; to take an active role in formulation of national electrical safety standards.

Major Findings: (1) Several areas of the Clinical Center contained ungrounded 250 volt receptacles which met code requirements when installed, but are considered hazardous by todays standards. (2) Clinical electrical equipment are in need of a preventative maintenance program to promote performance assurance and reduce equipment failures. (3) Clinical Center defibrillators are in need of a scheduled program of testing to assure their readiness for emergency use. The testing being performed presently is not sufficient and not all defibrillators are tested regularly.

Proposed Course: (1) To eliminate from the Clinical Center all ungrounded 250 volt receptacles and educate personnel regarding the hazard involved in their use. (2) To initiate a formal preventative maintenance program for performance assurance of clinical electrical equipment. The program should also reduce down time and failure rates. The equipment would be evaluated on an annual basis. (3) To establish a formal testing program for defibrillators with weekly testing of battery powered defibrillators and quarterly testing of line powered defibrillators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10015-05 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of Miniature Catheter for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	J.L. Doppman	Chief	DR CC

COOPERATING UNITS (if any)

DR-CC

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.25	.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A miniature toposcopic catheter attached to the end of a 1-mm #6 French catheter has been developed for insertion in tortuous blood vessels as small as 1 mm in diameter and up to 30 cm long. Catheter tests in anesthetized dogs have been highly successful - the catheter is able to penetrate parts of the vascular system which are unaccessible by existing techniques. The apparatus has been redesigned to provide the reliability and convenience required for clinical use. The catheter will enable the delivery of embolizing agents or other therapeutic substances so that some procedures previously requiring surgery can be performed instead with catheters. Techniques of steering the catheter are being developed and efforts are in progress to reduce the outer catheter size to #5 French and allow aspiration of fluid from remote areas.

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels and steering it into selected branches.

Develop techniques and devices for delivering therapeutic materials into the catheterized vessel for clinical usage and to aspirate fluids from these locations.

Major Findings: A miniature topographic catheter capable of negotiating tortuous paths has been successfully tested in dogs and will soon be ready for clinical use.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diameter vessels separated from larger, easily catheterized vessels by long, narrow passages with numerous bifurcations. The capability would permit selective treatment of tumors, aneurysms, and other lesions with minimal danger to normal tissues. Delivery of embolizing agents and materials to stain tissue, as well as aspiration of fluid, are contemplated.

Proposed Course: Complete construction and testing of the clinical apparatus and then use the system clinically. Develop steering techniques, test in animals, and incorporate into the existing system. Develop related devices and explore additional used for the catheter.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10018-05 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Particulate Hydrodynamics in Porous Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
	M.E. O'Neill	Reader Mathematics	Univ. Coll., London

COOPERATING UNITS (if any)

Department of Mathematics, University College, London

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models are being developed to describe passive membrane transport through pores or intracellular gap junctions. The Taylor-Aris dispersion analysis is extended to treat combined Brownian motion and convection in a single pore. The solute particle dimension is assumed to be large compared to that of the solvent molecules and also appreciable in size compared to that of the solvent molecules and also appreciable in size compared to the lateral pore dimension. The latter condition implies strong "hindered diffusion" and related solute-membrane interaction effects. A key aspect of the analysis is a generalized Einstein relation for predicting axial and radial components of the diffusivity tensor from hydrodynamics solutions for resistance coefficients. Perturbation techniques are used to obtain asymptomatic solutions to the hydrodynamic equations, and the method of moments is employed to analyze the solute continuity equation. Related hydrodynamic problems are also being considered, such as flow through constricted vessels.

Objectives: The objective of this project is to provide the basis for a rigorous, predictive continuum theory for passive transport phenomena in porous membranes, including such observations as "hindered diffusion". The development of solutions to hydrodynamic problems of interest in other areas of the biological and physical sciences is also considered.

Methods Employed: The essence of the approach to membrane transport is an extension of the Einstein continuum analysis for the Brownian motion of spherical molecules in dilute solutions. Einstein derived his predictive relation for the diffusion coefficient from the theoretical expression for the hydrodynamic resistance to translation of a rigid sphere through a homogenous viscous fluid of infinite extent. The continuum analysis for porous membranes begins with a single solute molecule in a single pore and assumes that the form of Einstein's relationship between the diffusion and resistance coefficients remains valid. However, the presence of the rigid pore wall, in general, increases the hydrodynamic resistance to translation and rotation of the solute relative to the fluid. The diffusivity is thereby decreased in magnitude until, in the limit, as the solute dimension becomes equal to the lateral pore dimension, the diffusion coefficient falls to zero. Where there is, in addition to diffusion, net movement of the fluid through the pore, the hydrodynamic interaction similarly affects the solute flux relative to the solvent flux. The project is concerned with deriving the requisite expressions for the resistance coefficients from hydrodynamic theory as well as developing analyses for diffusive and convective porous membrane transport.

The primary theoretical tools used in the hydrodynamic problems are regular and singular perturbation techniques (typically using the ratio of solute to pore dimensions as the asymptotic expansion parameter) and collocation techniques of the type developed by Weinbaum, and Pfeffer.

The transport analysis has been approached using the Taylor-Aris type dispersion treatment and the method of moments for deriving expressions for the pertinent coefficients without directly solving the complete solute continuity equation (convective-diffusion equation).

Major Findings: We completed the derivation of expressions correct to the second order in the sphere-to-tube radius ratio for the pressure drop due to the presence of neutral spherical solutes in cylindrical pores. Numerical computations using these expressions is proceeding.

An analysis was begun for describing the axisymmetric settling of a toroidal particle inside a vertical fluid-filled tube.

Proposed Course: In addition to the models presently under study, it would be desirable to examine a situation in which the solute is a nonspherical body in order to determine how to handle partical orientation and rotational Brownian motion effects. An ellipsoidal solute would be the likely choice in terms of posing theoretically tractable problems. Another direction to pursue, which would greatly extend the range of applications for the theory, would be to incorporate into the present models nonhydrodynamic solute-membrane interactions such as electrostatic or London Van der Waals attractive/repulsive forces.

Significance: Channels (pores, slitlike gap junctions) represent one important type of transmembrane transport in biological systems. A rigorous conceptual and predictive framework for pore theory would be useful in clarifying relevant biological transport and would find wide applicability in engineering and physical science work pertaining to synthetic membranes.

Publications:

Bungay, P.M. and O'Neill, M.E.: The pressure drop along a tube due to an axisymmetric constriction. J. Colloid Interface Science 71(2): 216-236, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10022-04 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes/pH Probe

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

H-IR-MH

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical and Mechanical Engineering Sections

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .25	PROFESSIONAL: .25	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In the initial year of the project, a miniature pH sensor, based on fiber optics, was designed to pass through a 22-gauge needle intended for implantation in tissue for physiological studies during exercise. The operation of the probe depends on pH changes identified by dye indicators. The probe is connected to laboratory optical instrumentation.

During the second year, an electro-optic measuring and readout system was designed and developed specifically for the pH sensors. The new unit makes the overall system portable, practical, and easy to use. In vitro tests were performed to characterize the pH sensor and the instrument. In the third year, improvements in the probe were made, and its applicability to blood pH determination was shown.

The effort during the current year was on improvement in the probe, aid to investigators interested in its application, and preparation of a publication.

Objectives: Develop a pH sensor for tissue implantation to be used in studies of oxygen transport during exercise.

Methods Employed: A fiber optic measurement of dye indicator response to pH.

Significance: In studies of abnormality in transport of oxygen to tissue by blood during exercise, measurements of oxygen pressure in the tissue can be used to determine the oxygen content of the blood supply via the blood oxygen saturation curve (concentration vs. pressure). Alternately, measurements of the blood oxygen concentration can be used to determine oxygen pressure by this curve. Since the relation between oxygen pressure and concentration is affected by changes in pH which occur during exercise (shift in the curve with pH, the Bohr effect), it is necessary to incorporate a pH measurement with the oxygen measurement in making use of the curve.

The probe is also potentially useful for clinical application in monitoring blood and tissue pH in heart surgery and other intensive care situations.

Publications:

Peterson, J.I., Goldstein, S.R., Fitzgerald, R.V. and Buckhold, D.K.: A fiber optic pH probe for physiological use. Analytical Chemistry 52: 864, 1980.

Goldstein, S.R., Peterson, J.I. and Fitzgerald, R.V.: A miniature fiber optic pH sensor for physiological use. ASME Transactions, Journal of Biomechanical Engineering 102: 141, 1980.

Further work on the pH probe is not planned.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10023-04 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Two-Dimensional Ultrasonic Imaging System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	W.S. Friauf	Chief	EEES BEIB DRS
	T.E. Hall	Electronic Engineer	BEIB DRS
	J.L. Doppman	Chief	DR CC
	T.H. Shawker	Clinical Associate	DR CC
	W.C. Whitehouse	Electronic Technician	ADM CC

COOPERATING UNITS (if any)

DR-CC; ADM-CC

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c) NEITHER]

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several subsystems of a comprehensive, versatile, ultrasonic imaging and recording system have been developed. A second-generation real-time mechanical sector scanner has been put into use along with a video system for consolidation, displaying, and recording a variety of data. The development of a solid-state sector-to-TV scan converter is completed. The overall system has proved to be especially useful in abdominal scanning and early detection of pregnancy. It is now also being employed for tongue motion in a voice study.

PHS-6040
(Rev. 10-76)

Objectives: Development of a high-performance two-dimension real-time ultrasonic imaging system with provision for a standard TV output to facilitate video tape recording of an examination, including the sector, a view of the patient, real-time clock, additional alpha numeric information, moving trace ECG and pressure data, voice commentary. Additional objectives are versatility, that is, suitability for ocular, cardiac, pediatric, and abdominal scanning with minor changes, and high benefit/cost ratio.

Methods Employed: Based on the positive results obtained with the mechanical scanner designed and built earlier, a second-generation mechanical sector scanner was developed. The size of the scanner and mechanical vibration have been substantially reduced. In addition, the new scanner maintains electrical control of the scan pattern through the use of position feedback, which provides three major advantages relative to earlier mechanical scanners: (a) lines are spaced uniformly throughout the sector; (b) synchronization with standard TV systems is easy--a feature which facilitates high-quality imaging in video format.

For the purpose of building up a TV picture with many types of information simultaneously for recording via video tape, appropriate commercial components have been assembled into a system.

Publications:

Dunnick, N.R., Schuette, W.H. and Shawker, T.H.: Ultrasonic demonstration of thrombus in the common carotid artery. AJR 133, 544-545, September, 1979.

Shawker, T.H., Schuette, W.H., Whitehouse, W., and Rifka, S.M.: Early fetal movement: A real-time ultrasound study. Obstetrics and Gynecology, Vol. 55(2), February, 1980.

Shawker, T.H., Schuette, W.H. and Whitehouse, W.: Overhead TV camera: Useful addition to ultrasonic laboratory. AJR 134: 608-609, March, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10027-04 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of Whole-Body Hyperthermia Instrumentation and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	J. Bull	Senior Investigator	MC DCT NCI
	D. Lees	Staff Anesthesia	CC NIH
	J. Whang Peng	Senior Investigator	MS DCT NCI
	R. Corsey	Electronic Engineer	BEIB DRS
	H. Tipton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

MC-DCT-NCI; CC-NIH; MS-DCT-NIH

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Whole body hyperthermia is being studied at NIH as a possible means of treatment for cancer. This project includes development of an instrumentation and control ssytem based on utilization of a Tektronix 31 programmable calculator, digital plotter, and interface for data acquisition. The esophageal temperature of the patient is regulated to 0.1°C accuracy by feedback control of the temperature of water circulating in a set of hyperthermia blankets. This project was comleted August 1980, however additional publications have been made.

Methods Employed: A Tektronix 31 programmable calculator is being used to acquire, record, and process data as well as to control water temperature of a set of hyperthermia blankets. The temperature of the water pumped through the blankets together with esophageal and rectal temperatures of the patient are processed by the calculator, which then develops temperature commands for the water temperature mixing valve. The mixing valve adds hot or cold water to the flow stream returning from the blankets as directed by the Tektronix digital interface unit so that heart rate, blood pressure, and temperature data could be processed by the system. The multiplexer module also provides commands from the calculator to the water mixing valve motor. Automatic cool-downs are programmed into the calculator in response to various out-of-limit conditions. The calculator functions in an interactive mode for entry of operational instructions.

Major Findings: The major finding from the use of the equipment is that it is possible to take the whole-body core temperature of patients to 42.0 ±0.1°C for four hours on a biweekly basis without major difficulty. The finding suggests that hyperthermia treatment for cancer is practical. Currently, the system is being employed in conjunction with chemotherapy.

Publications:

Bistoni, F., Lees, D.E., Bull, J.M., Baskies, A.M., Chretien, P.B., Smith, R., Whang-Peng, J., Schuette, W.H. and DeVita, V.T. Correlation of Serum Glycoproteins and Blood T-cell Levels with Clinical Course During Whole Body Hyperthermia (WBHT) Alone or with Chemotherapy. Proceedings of 15th American Society Clinical Oncology, New Orleans, May 14-15, 1979, p. 194.

Bull, J.M., Whang-Peng, J., Lees, D.E., Smith, R., Schuette, W.H., Kim, Y.D., DeVita, V.E. Phase I Trial of Systemic Heat and Adriamycin. Proceedings of 15th American Society Clinical Oncology, New Orleans, May 14-15, 1979, p. 398.

Kim, Y.D., Lees, D.E., Lake, C.R., Whang-Peng, J., Schuette, W.H., Smith, R., and Bull, J. Hyperthermia Potentiates Doxorubicin-Related Cardiotoxic Effects. JAMA 241(17), April 27, 1979.

Lees, D.E., Kim, Y.D., Schuette, W.H. and Macnamara, T.E. Auscultatory Confirmation of Placement of Esophageal Temperature Probe. Anes. Rev. 35, August, 1979.

Kim, Y.D., Lake, R., Lees, D.E., Schuette, W.H., Bull, J.M., Weise, V., and Kopin, I.J.: Hemodynamic and Plasma Catecholamine Responses to Hyperthermic Cancer Therapy in Humans. American Journal of Physiology 237(5), pp. H570-H574, 1979.

Lees, D.E. and Schuette, W.H.: Microwave Rewarming. Anesthesia and Analgesia, Vol. 59(2), 161, 1980.

Lees, D.E., Kim, Y.D., Bull, J.M., Whang-Peng, J., Schuette, W., Smith, R., and Macnamara, T.E.: Anesthetic Management of Whole-Body Hyperthermia for the Treatment of Cancer. Anesthesiology 52: 418-428, 1980.

Bull, J.M., Lees, D.E., Smith, R., Schuette, W.H., Katin, M., Glatstein, E., and Devita, V.T.: Whole Body Hyperthermia (WBH) Combined with Nitrosourea in Malignant Melanoma. Proc. ASCO Meeting, March, 1980, San Diego, CA.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10034-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Three-Dimensional Histological Reconstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .5	PROFESSIONAL: .45	OTHER: .05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c) NEITHER]

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A semi-automatic system for acquisition of three-dimensional structural information about histological material is being developed. The system should have significant speed and reliability advantages over present techniques using serial sections, although resolution may be limited. In brief, an embedded tissue block will be fixed relative to a scanning electron microscope imaging system, the surface of the block will be imaged and stored, and successive slices will be removed by a built-in microtome. Handling and registration of thin sections will thus be eliminated. Human and computer pattern recognition will transform the resulting set of images into a three-dimensional reconstruction.

Objectives: (1) To facilitate making schematic diagrams of neural nets. (2) To facilitate developmental studies of small organs and organisms.

Methods Employed: Various cutting, staining, and imaging techniques are being evaluated for best resolution.

Major Findings: So far, the feasibility of the project has been demonstrated in that resolution of 600 Angstroms has been achieved on cut faces of Epon embedded neural material in the SEM. Construction of the miniature microtome is complete.

Significance: Neuroanatomists may be able to trace significant neural nets easily enough to do enough samples to be statistically significant.

Proposed Course: The miniature microtome will be bench tested to verify proper cutting mechanics and general operation. The unit will be integrated with a scanning electron microscope and cutting will be tested in a vacuum. Finally, the entire system will be integrated with a computer for semi-automatic reconstructions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10039-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Biophysical Instrumentation and Methodology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHER:	T.R. Clem	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c)] NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project is designed to develop new instrumentation and methodology or improve existing instrumentation and methodology for characterization of biological macromolecules. Analytical ultracentrifugation and techniques ancillary to it are the major areas of interest.

Objectives: To develop data acquisition systems for analytical ultracentrifuges and for ancillary equipment such as plate or film readers and densimeters and to develop appropriate software to use with the acquisition systems.

Methods Employed: A microprocessor controlled data acquisition system has been developed for use with the Anton Paar densimeter which is used for the determination of solution densities needed for the calculation of partial specific volumes required for the determination of molecular weights from ultracentrifuge data. This acquisition system controls the operation of the densimeter, records data acquired from it, calculates current means and standard deviations and prints all of these values. Thus, once a sample has been introduced into the instrument, operation is entirely automatic until the investigator, on the basis of the printed values of the means and standard deviations, decides that the measurement has been made to the desired level of precision. This has simultaneously resulted in increasing the attained level of precision and in greatly reducing the amount of time the investigator has to spend in obtaining good data. Microprocessor controlled data acquisition systems for the analytical ultracentrifuge and for the plate and film reader used with the ultracentrifuge are presently under development. These will be controlled by a microcomputer which will also be used to store data, do preliminary calculations and editing, and then transmit the data to the DEC-10 computer for further processing which would be beyond the capabilities of the microcomputer.

Significance: The data acquisition system for the densimeter has already greatly facilitated the use of this instrument, resulting in the greatly improved acquisition of data from this instrument with a very marked diminution in the time required of the investigator and a significant improvement in the precision of the densities obtained. Since data acquisition has been the limiting factor in terms of the qualitative and quantitative aspects of ultracentrifuge research, it is anticipated that the development of the data acquisition systems described above will greatly facilitate such research.

Proposed Course: Continue the developments outlined above.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10040-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Physical Chemistry of Biological Macromolecules

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHER:	R.S. Adelstein	Section Chief	CB NHLBI
	S.I. Chung	Research Chemist	LB NIDR
	G. Felsenfeld	Section Chief	LMB NIAMDD
	J.S. Finlayson	Director	PDB BB
	J.A. Gladner	Research Chemist	LCB NIAMDD
	A.P. Minton	Research Chemist	LCB NIAMDD
	J.C. Osborne	Research Chemist	MD NHLBI
	R. Shrager	Mathematician	LSMM DCRT
	J. Waters	Physical Sciences Aide	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.1	PROFESSIONAL: 0.9	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES x☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the physical properties of a wide variety of biological macromolecules with the goal of correlating these properties to the structure and function of the macromolecules. The emphasis is on molecular size and shape, the thermodynamics of molecular interactions, and on molecular weight distributions. Analytical ultracentrifugation and mathematical modelling are the principal research techniques used.

Objectives: (1) To study the ultracentrifugal behavior of myosin phosphatase. (2) To study the anomalous partial specific volume of lamprey fibrinogen in 6 molar guanidine hydrochloride buffer. (3) To study the nature of density gradients of high concentrations of dextrans in the ultracentrifuge. (4) To study the ultracentrifugal behavior of the D-fragment of human fibrinogen. (5) To study the ultracentrifugal behavior of hemoglobin and myoglobin at physiological concentrations. (6) To study the effects of surface activity on solute distribution in the ultracentrifuge. (7) To study the effectiveness of mathematical modelling in discriminating between correct and impostor models for fitting ultracentrifuge data. (8) To study methods for the analysis of molecular weight distributions from ultracentrifuge data.

Methods Employed: The various macromolecules have been isolated and purified from appropriate sources by conventional means or have been prepared synthetically. The molecular weights have been determined by analytical ultracentrifugation and the resultant data has been analyzed by mathematical modelling techniques using the MLAB system on the DEC-10 computer. Mathematical modeling techniques have also been used for studies of molecular weight distribution and for studies on fitting ultracentrifuge data. Partial specific volumes have been studied by densimetric techniques.

Major Findings: Preliminary studies on myosin phosphatase appear to indicate that this enzyme undergoes a reversible association as a monomer-dimer-tetramer. Studies are now underway to investigate this possibility and to determine the thermodynamic parameters of the association.

Studies on lamprey fibrinogen indicated that the partial specific volume of this macromolecule changed in an anomalous manner when the fibrinogen was dissolved in 6 molar guanidine buffer. This change was deduced from ultracentrifugal data. It is now being verified by densimetric studies which directly measure the partial specific volume of the fibrinogen in normal buffers and in 6 molar guanidine buffers.

The ultracentrifugal density gradients of various dextrans as functions of loading concentration and rotor speed were determined. This required the measurement of concentration distributions of high concentrations of dextrans and also densimetric measurement of the partial specific volumes of the dextrans. Equations were derived which would accurately predict the densities of the different dextrans as functions of position in the ultracentrifuge cell given the loading concentration, the rotor speed, and the positions of the solution meniscus and bottom in the cell.

Studies on the D-fragment of human fibrinogen show that preparations which have not been in contact with any denaturing solvents such as high concentrations of urea of guanidine are homogenous, do not exhibit any aggregative behavior, and have a molecular weight of 120,000 daltons.

The ultracentrifugal behavior of myoglobin and hemoglobin at very high concentrations has been studied in order to determine whether or not myoglobin undergoes any associative reaction at physiological concentrations. The very great optical densities of such solutions which were at concentrations as high as 35% required devising 0.1 mm thick centerpieces for the ultracentrifuge cells. The problem of possible association of the myoglobin being masked by the marked thermodynamic non-ideality at high concentrations was treated by studying the ratios of the apparent molecular weights of myoglobin and hemoglobin as functions of concentration, since both are hemoproteins with very similar monomer molecular weights and the associative behavior of hemoglobin is well known. The data strongly suggests that myoglobin associates at least to form a dimer and that further association might be possible. Additional studies are being planned to further elucidate this possible association.

Studies on plasma apolipoproteins showed that they exhibited a significant level of surface activity and also that this surface activity might result in anomalies of concentration distribution in the ultracentrifuge cell. A thermodynamic theory for the effect of surface activity on concentration distribution was derived and mathematical modelling showed that the effect was of a significant magnitude under certain experimental conditions. The application of this theory to the experimental data is now in progress.

Mathematical modelling has been used to determine how well this technique can be used to determine an appropriate model of an associating system. This has been done by generating simulated data for a specific model, adding experimental noise, and then comparing the fits of the correct model and of imposter models. It has been shown that in almost all cases, if the experiment is properly designed, it is possible to discriminate between correct and impostor models. This study has been useful also in determining the factors in experimental design which optimize the discrimination between models.

Studies on obtaining molecular weight distributions from ultracentrifugal data have involved determination of the necessary criteria for obtaining these distributions using regularization techniques. In spite of having some success in fitting symmetrical and skewed unimodal distributions, the lack of success we have had in fitting any more complex distributions has convinced us that this problem is mathematically too ill-conditioned for this approach to succeed. We are now attempting to determine whether it is possible to determine a distribution by comparing the concentration distribution associated with a particular molecular weight distribution with an experimentally obtained concentration distribution using the criteria found appliable in the studies on associating systems.

Significance: The studies on the fibrinogens and their fragments are relevant to a basic understanding of their antigenicity and to the action of plasmin on fibrinogen; these all relate to the role of fibrinogen in normal and pathological blood clotting. The studies on myosin phosphorylase are relevant to the role of this enzyme to the mechanism of myosin in muscle concentration. The studies on the density distributions of dextrans is significant because these are used in ultracentrifugal studies of the physical properties of nucleosomes. The studies on the surface properties of the plasma apolipoproteins are relevant to the interaction of these proteins with plasma lipids. The studies of myoglobin at high concentrations is relevant to the behavior of the oxygen-binding hemeproteins at physiological concentrations. The mathematical modelling studies are of importance because they enhance our abilities to successfully deal with these problems in the physical chemistry of macromolecules.

Proposed Course: The manuscript on lamprey fibrinogen will be revised to incorporate the new data on partial specific volumes. Manuscripts on the effects of surface activity of plasma apolipoproteins, on mathematical modelling studies on associating systems, and on the behavior of myoglobin at physiological concentrations have been started. Further studies on myoglobin, fibrinogens, and on myosin phosphorylase are planned. The mathematical modelling studies on molecular weight distributions will be continued. New studies on modified hemoglobins, natural and synthetic detergents, and on various protein interactions are planned.

Publications:

Davies, P.J.A., Wallach, D., Willingham, M., Pastan, I., and Lewis, M.S.: Self-association of chicken gizzard filamin and heavy merofilamin. Biochemistry 19, 1366-1372, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 10041-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Flow Visualization Studies and Hemodynamic Events in Model Arteries

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
OTHER:	R.L. Dedrick	Chief	ChES BEIB DRS
	D.L. Fry	Chief	H IR OD

COOPERATING UNITS (if any)

OD - IR - NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.7	PROFESSIONAL: 0.4	OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The appearance of atherosclerotic lesions at specific locations in the arterial tree has led many investigators to study the relevance of hemodynamic factors in atherogenesis. The purpose of this study is to investigate the patterns of flow in models of arterial geometry to measure velocity profile at several cross sections, and to seek correlations between fluid mechanic events and the development of atherosclerotic plaques. In previous studies, quantitative measurements of the wall shear stress were made in model arteries by an electrochemical technique. However, the work provided no information about the direction of the shearing forces, and little idea about the nature of the flow patterns. In this study various methods of flow visualization such as dye injection, neutrally buoyant microsphere tracers and laser illuminated light scattering particles are being used to study the flow patterns in arterial models as a function of various flow parameters such as Reynolds number, branch flow ratios, and pulsatility. Both still photography and high-speed cinematography record the flow phenomena. The electrochemical technique measures average mass transfer coefficients to the artery wall under conditions of steady and pulsatile flow.

PHS-6040
(Rev. 10-76)

Objectives: The objectives of this study are to visualize and record the various kinds of flow phenomena such as flow separation and secondary flow that may occur in complex flow channels that represent arterial geometry and to correlate the flow phenomena with the location of atherosclerotic plaques in experimental animals. The analysis will include a quantitative measure of the velocity profiles at various sites in the model arteries. In conjunction with these experiments, measurements will be made of the mass transfer coefficients to the walls of the model arteries under conditions of both steady and pulsatile flow.

Methods Employed: Several methods have already been shown to be useful for visualizing flow patterns in our model systems, and other methods can be tried. The electrochemical method of measuring mass transfer coefficients is being used in several model systems. The following techniques are being used.

(1) Dye injection. At selected sites in the arterial model, small ports are drilled for insertion of #30 gauge hypodermic tubing, which is connected via PE 10 catheter tubing to a reservoir of colored dye. The end of the hypodermic tubing can be positioned at any radial location in the flow model and the dye slowly injected into the flow to mark the streamlines. The streamline patterns at several sites are then recorded using 35-mm still photography. Data obtained by dye injection into the flow indicates that the flow streamlines are skewed toward the side-arm branches exiting from the main (aortic) flow channel and that unusual patterns of backflow and secondary flow occur near the dorsal channel wall just opposite the branch orifices. These phenomena are governed by the fraction of the flow that exits out each daughter branch.

(2) Neutrally buoyant microspheres. This method employs a dilute suspension of 100- to 500-micron diameter polystyrene microspheres in a 20 to 25 percent glycerine/water solution, which serves as the test fluid in the flow model. The microspheres are dyed with a fluorescent dye and then illuminated with ultraviolet light making them clearly visible in the flow system. The path of the microspheres are photographed with high-speed cinematography as these neutrally buoyant particles move along with the fluid. In such a manner, the direction and velocity of fluid elements can be determined. This method gives an overall view of the flow patterns throughout the bulk of the fluid flow.

(3) Laser Doppler velocimetry. When light is scattered from a moving object, a stationary observer will see a change in the frequency of the scattered light (Doppler shift) proportional to the velocity of the object. This Doppler shift is used to measure the velocity of particles at various locations in the fluid. From the particle velocity, the fluid velocity is inferred. A laser is used as the light source because it is easily focused and coherent. This method allows us to determine, quantitatively, the velocity profiles at various positions in the arterial model. Numerous profiles have been recorded in both steady and sinusoidal flow at various flow rates.

By passing the thin collimated laser beam through a cylindrical lens, a source of plane illumination can be created which can be usd to visualize a specific narrow cross section in the flow channel by observing its light scattering effect from small particles that move with the fluid. This technique exhibits, in two dimensions, various flow patterns like stream lines and separation eddies.

Significance: Elucidation of the role of hemodynamics on the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease. Certain biological evidence suggest that areas of increased plaque formation may correlate with areas frequently exposed to disturbed flow, for example, flow separation, or to relatively stable flow patterns that change direction and magnitude periodically throughout the day with varying metabolic and blood flow demands. This study should demonstrate various types of flow patterns that can occur in arterial systems as a function of changing flow parameters. Likewise, the mass transfer of blood borne constituents like oxygen or lipoproteins can be affected by the flow patterns in various regions near the artery wall. An imbalance in the mass transfer of these elements can cause either vascular damage or excess accumulation of lipids which can eventually lead to a pathological state in the artery wall.

Proposed Course: (1) Study the flow patterns in these models using the various techniques described above as a function of several flow parameters such as Reynolds number, branch flow ratio, and flow pulse frequency. (2) Correlate these findings with those of our previous experiments on wall shear stress in similar models. (3) Determine the mass transfer coefficients to the arterial wall as a function of various Schmidt numbers under conditions of steady and pulsatile flow. (4) Correlate all hemodynamic evidence with incidence of lesions in experimental animals.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10043-03 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes/Oxygen Probes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .75	PROFESSIONAL: .75	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Successful development of a fiber optic pH probe has provided a model for the construction of other probes, the most important being an oxygen probe. The original approach taken for development of an oxygen probe was to find or develop a suitable reversible color indicator. Our attempts were unsuccessful, so effort starting last year and continuing through this year has been on adaptation of the principle of fluorescence quenching by oxygen.

PHS-6040
(Rev. 10-76)

Objectives: Develop an oxygen sensor for tissue implantation to be used in studies of oxygen transport during exercise, and clinical Po_2 measurements.

Methods Employed: A fiber optic measurement of dye-indicator response to oxygen by fluorescence quenching.

Significance: Po_2 measurements are fundamental to understanding and control of oxygen transport in research and clinical investigations. Measurements on withdrawn blood samples lack convenience, reliability, and relevance to many situations of interest. Indirect estimation of Po_2 using spectrophotometric measurements of hemoglobin oxygenation and the concentration-pressure transfer function (blood oxygen saturation curve) is subject to too many uncertain variables. Development of a fiber optic Po_2 probe would represent a significant advance in the ability to directly measure blood and tissue oxygen. A satisfactory electrode for general use has never been developed, and the fiber optic approach offers some distinct advantages in small size, flexibility, and safety.

Major Findings and Proposed Course: Fluorescence or phosphorescence quenching by oxygen is one of the most sensitive techniques available for oxygen measurement, but it is not directly applicable to use in a fiber optic probe without the resolution of three major problems: (1) the availability of a dye which combines sufficient sensitivity with long wavelength ($>$ 450nm) excitation; (2) a water-vapor insensitive support for the dye which maintains its sensitivity to oxygen; and (3) a suitable highly oxygen permeable hydrophobic envelope for the probe. These problems have been solved, although there is room for improvement in item 2, the support. Current and continuing work is devoted to evaluation of probes constructed on this basis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10050-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Positron Emission Tomography Scanner

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. DiChiro	Section Chief	SN NINCDS
OTHER:	R.A. Brooks	Senior Staff Fellow	SN NINCDS
	V.J. Sank	Research Physicist	SN NINCDS
	W.S. Friauf	Electronics Engineer	EEESBEIBDRS
	S.L. Leighton	Mechanical Engineer	MES BEIB DRS
	H.E. Cascio	Electronics Engineer	EEESBEIBDRS
	G.L. Hemphill	Electronics Technician	EEESBEIBDRS

COOPERATING UNITS (if any)

SN NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
EEES, MES

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.7	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A custom PET scanner is being developed to provide compromises between resolution, sensitivity, count rate capability, and cost that are optimal for human neurological research requirements at NIH.

Objectives: Design and have built a PET scanner with higher resolution than other custom or commercial machines, but without excessive compromise of sensitivity or count rate capability.

Methods Employed: The design will feature a large number of BGO detectors more tightly packed in a smaller ring than other designs, with electronic advances to shorten the coincidence window to a minimum, thus easing the random coincidence problem which is aggravated by a small ring. A novel detector motion has been developed to further improve resolution.

Major Findings: The detector ring and associated electronics have been designed at NIH and built by contractors. The electronics delivered to date will allow operation with 1 slice; this will be increased to 7 when the system is complete. A computer and display system have been purchased and software is under development here.

The mechanical system for providing the circular translation motion for the detecors has been designed and fabricated by BEIB. The 350 pound detector assembly can be indexed 45 degrees in 0.4 seconds or moved continuously at the required 30 rpm. A truss structure has been completed which supports the detector and tilts its plane of motion at any angle from vertical to horizontal to suit supine or seated patients. A unique spring counter balance mechanism removes the gravitational load from the indexing drive, thereby allowing the use of a small motor which is only required to overcome frictional and inertial forces.

A two channel system for experimental studies was constructed using prototype versions of all critical electronic components, including detector assemblies, preamps, discriminators, and coincidence detectors. The experimental work has verified that the design should meet all program objectives.

Significance: PET imaging with a variety of positron emitting tracers allows many metabolic processes to be studied spatially. The new scanner will increase the spatial resolution which currently limits the potential of the approach.

Publications:

Brooks, R.A., Sank, V.J., DiChiro, G., Friauf, W.S., and Leighton, S.B.: "Design of a High Resolution Positron Emission Tomograph: The Neuro-PET. Journal of Computer Assisted Tomography 4(1): 5-13, February, 1980.

Brooks, R.A., Sank, V.J., Friauf, W.S., Leighton, S.B., Cascio, H.E., and DiChiro, G.: Design Considerations for Positron Emission Tomography. IEEE Transactions Biomed. Eng. Nov., 1980, in press.

Invention Reports: Four have been submitted.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10051-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Monolithic Thermopile

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.S. Friauf	Electrical Engineer	EEES BEIB DRS
OTHER:	C. Mudd	Mechanical Engineer	MES BEIB DRS
	R. Berger	Section Chief	LTD NHLBI

COOPERATING UNITS (if any)

NBS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.4	PROFESSIONAL: 0.2	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (x) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Process technology developed by the semiconductor industry should be ideal for thermopile fabrication, allowing advances in micro-calorimetry with many applications to biomedical research.

Objectives: Develop a monolithic thermopile for use in micro-calorimeters in place of conventional thermopiles, in order to enhance speed and sensitivity of thermal measurements of reaction kinetics.

Methods Employed: A device has been designed and several batches have been fabricated by NBS on contract. The design is intended to provide good sensitivity with greatly reduced thermal mass and conductivity.

Major Findings and Proposed Course: The first batches of devices work and show considerable promise. However, there have been reliability problems due to the fragility of the devices; hopefully these can be solved by improved mounting techniques. Overall performance is limited by the value of polysilicon sheet resistance obtainable. The performance of random access memories is limited by the same factor, so intensive R and D is being devoted to the problem. It appears that laser annealing may afford a marked improvement and will be investigated.

The present devices, as well as improved ones obtained later, will be incorporated into a micro-calorimeter for more complete evaluation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10053-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Membrane Based Sampling Systems for in In Vivo and In Vitro Kinetic Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	J.P. Froehlich	Senior Investigator	GRC NIA
	R.L. Berger	Section Chief	LTD NHLBI
	J. Fenstermacher	Section Chief	LCHPH DCT
	R.L. Dedrick	Section Chief	ChES BEIB DRS
	P. Krindel	Guest Worker	ChES BEIB DRS

COOPERATING UNITS (if any)

Gerontology Research Center-NIA; Laboratory of Technical Development-NHLBI; Laboratory of Chemical Pharmacology-DCT.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Synthetic membranes are being utilized in kinetics studies to provide a means for continuous sampling of the liquid phases from systems in which a dispersed particulate phase is suspended in the liquid phase. In one application sampling equipment is being developed for in vitro study of calcium ion transport and calcium-ATPase activity in suspension of sarcoplasmic reticulum vesicles prepared from homogenates of rabbit muscle. In a second application a study of the mammalian blood-brain-barrier permeability is being aided by the development of an apparatus incorporating a sampler in an arteriovenous ex vivo shunt. In the latter plasmapheresis application pooling the plasma filtrate yields a single sample from which the plasma concentration times time integral can be evaluated for a chemical administered to the animal. Such sampling systems can be useful for the study of the kinetics of other fluid phase systems for which a membrane can be found which is permeable to one chemical of interest but impermeable to another necessary reagent or sink. Thus, other applications might be found in the areas of enzyme kinetics, pharmacokinetics, and the membrane transport of vesicle and cell suspensions.

Objectives: The principal objective is the development of the capability for fluid sampling based upon synthetic membrane technology. In many potential applications sampling by filtration or ultrafiltration may be more appropriate than alternative sampling technique. Ultrafiltration membranes allow the formation of samples representative of the free concentration of small soluble substances. These membranes will retain within the system under study macromolecules and those substances which are bound to them as well as colloidal or cellular components of the system. Other applications may call for the use of larger pore diameter membranes of, for example, macromolecules are to be sampled as well.

Methods Employed: The sampling system generally consists of three elements: (1) a module or modules containing sampling membranes, (2) sample collection equipment, and (3) a means for controlling the rate of production of sample. The membrane module is designed so that the membrane forms a part of the wall of the channel through which the liquid to be sampled flows. Only a small fraction of the liquid is diverted across the membrane to form the sample. The sample is produced as a consequence of a difference in pressure imposed across the membrane. The rate of production of the sample is regulated either by controlling the transmembrane pressure difference or through use of a sample metering pump.

Significance: Membrane sampling is being applied to studies of the transport of calcium ions across sarcoplasmic reticulum (SR). The transport studies are performed in vitro on a suspension of SR vesicles in buffer; the vesicles being created by homogenizing rabbit muscle. The kinetics of calcium uptake by or efflux from the vesicles can be followed by monitoring the appearance or disappearance of calcium from the suspending medium. Also, changes in levels of ATP and inorganic phosphate can be used to infer the kinetics of the calcium dependent membrane ATPase. The membrane in the sampler retains the vesicles (which are thought to be in the range of 0.1-0.5 m in diameter), so that the sample is representative of the suspending media.

A second application concerns in vivo studies of transport across the blood-brain-barrier. The initial objective is the determination of the barrier permeability to selected marker substances. In these experiments a sampler is connected in line with an extracorporeal arteriovenous shunt. By continuously and steadily drawing off a fraction of the shunt flow through the sampler membrane, one can integrate over time the concentration of the marker substances present in the plasma. The value of the integral, together with a determination of the amount of the substance taken up by the brain over the same time interval, permits a determination of the permeability-area transport coefficient. A membrane which retains blood cells is of use in studies in which the transport of the substance into blood cells is sufficiently slow that the cells cannot be considered in equilibrium with the plasma. Use of ultrafiltration membranes may permit determination of the free concentration - time integral, rather than the integral for total plasma concentration, in circumstances of significant binding to plasma proteins.

The in vivo sampling technique can be applied to other acute pharmacokinetic studies for which the plasma concentration-time integral can be of use.

Major Findings: During the current year we conducted a series of experiments to quantify the degree to which the SR vesicles remain intact under the flow conditions to which they will be subjected in the transport studies. We have also conducted studies of the kinetics of calcium binding to SR vesicles. These latter studies have revealed technical problems with the use of the membrane-based samplers which we are presently attempting to overcome.

A premise underlying the concept of filtration sampling is that the marker substance appears in the filtrate (sample) solely because it is carried convectively across the membrane. However, when the plasma concentration of the marker is changing sufficiently rapidly with time, thereby generating spatial gradients in the filtrate tracer concentration, marker diffusion across the membrane and the membrane support can diminish or augment the amount of marker present in the sample. If the filtrate flow rate is sufficiently high or the diffusivity of the marker is small the diffusional contribution should be negligble compared to that from convection. We have been simulating the in vivo animal pharmacokinetic experiments using dye solutions and a sheet membrane module in an in vitro set-up. These simulations are attempting to quantify the conditions under which the sample is representative of the blood plasma kinetics.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10054-02 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Biomechanical Study of the Impairment of Wound Healing as a Consequence of a Variety of Cancer Therapies.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
OTHER:	T. Talbot	Mechanical Engineer	ACES BEIB DRS
	B. Shamberger	Clinical Associate	SURG. NCI
	M. Brennan	Senior Scientist	SURG. NCI

COOPERATING UNITS (if any)

SURG., NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Clinical impression suggests that Adriamycin interferes with wound healing. Biomechanical and biochemical studies of wound healing in the rat have been undertaken. Thus far, we have shown that wound breaking strength is significantly reduced when adriamycin accompanies surgery up to three days post-op. Delaying administration of adriamycin by seven days post-op eliminates the deleterious effect.

It appears that the defect contributing to reduced wound breaking strength in adriamycin treated animals is not due to a collagen maturation defect but is due to a reduction in scar collagen accumulation as measured by "new" hydroxyproline content and reduced fiber diameter as determined by EM measurements.

Previous reports intimated accelerated wound breaking strength by ultrasonic insonation. Four consecutive experiments with insonated and control groups of wounded rats failed to demonstrate this hypothesis.

Objectives: To study effects of a variety of cancer therapy protocols on wound healing, and to attempt to elucidate the underlying mechanism of any such deleterious results.

Methods Employed: Biomechanical studies are both analytical and experimental in nature. Tissue stress-strain relationships are obtained from an Instron tensile testing machine. Biochemical determinations and electron microscopy are performed simultaneously with the biomechanics.

Significance: Results of the study may lead to modified clinical protocols with the intention of promoting wound healing, thereby improving post-operative recovery.

Proposed Course: To study in detail the constitutive behavior of the healing wound.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10055-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Breath by Breath Analysis of Computer Controlled Exercise Stress Testing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	T. Talbot	Mechanical Engineer	ACES BEIB DRS
	H. Tipton	Mechanical Engineer (Tech.)	ACES BEIB DRS
	R. Winslow	Sr. Scientist	IR-CL-NHLBI

COOPERATING UNITS (if any)

IR-CL-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.4	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In recent years exercise stress testing has become an important diagnostic tool. Most testing of this type is confined to cardiac studies. This system has been developed in order to assess the ability of the subject to transport and exchange oxygen and carbon dioxide between the atmosphere and the cells of the body. A large number of pathophysiologic states limit one's ability to perform these functions efficiently. With this system the anaerobic threshold of the subject during exercise can be detected non-invasively by breath-by-breath respiratory analysis. Oxygen Uptake, Carbon Dioxide Production, Respiratory Minute Volume, Respiration Rate, Heart Rate, and Respiratory Quotion are displayed as a function of Work Rate.

Objectives: To develop a system to analyze the respiratory quotient vs. work rate curve during exercise stress testing in order to determine the anaerobic threshold.

Methods Employed: A Tektronix 4051 programmable calculator and custom designed synchronous integrators and multiplexor has been used to produce breath-by-breath analysis of respiratory quotient as a function of work rate.

Significance: Correlation of the onset of anaerobic metabolism with work level provides a useful clinical measure of the general condition of the hematology patients under study. This method provides a better means of evaluating the efficacy of therapeutic measures.

Proposed Course: To add a pressure transducer to the mouthpiece in order to obtain respiratory power and work.

Publications:

Talbot, T.L., Thibault, L.E., Schuette, W.H., Winslow, R.M., and Tipton, H.W.: Breath-by-breath gas analysis during exercise stress testing. Advances in Bioengineering, 1979.

Schuette, W., Thibault, L., Talbot, T., and Tipton, H.: Synchronous integration - a method for the rapid determination of the mean value of pulsatile physiological signals. Proc. AAMI 15th Annual Meeting, San Francisco, April 13-17, 1980, p. 184.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10057-02 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of NMR Imaging Magnet

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	D. Hoult	Electrical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: .7	OTHER: .8

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A novel magnet suitable for nuclear magnetic resonance (NMR) imaging has been designed, and constructed. The magnet employs windings on two hemispherical shells which can be rotated with respect to each other about two orthogonal axes. This arrangement allows prescribed large gradients in magnetic field to be superimposed on an initially homogenous field. The magnet dissipates 7.5 kw of power and has an inner spherical diameter of 0.6 m. Its two power supplies have a short term stability of better than 1 ppm over 10 seconds, and a long term stability of better than 10 ppm. The basic homogeneity of the magnetic field is about 50 ppm over a sphere of diameter 10 cms.

Objectives: To provide a large scale magnet suitable for exploring medical application of NMR imaging. The size of the device will permit examination of babies for detecting fluid filled lesions.

Methods Employed: A magnet consisting of two hemispherical shells each containing two separate windings was constructed. The shells are aluminum castings of 0.67 m diameter with radial flanges projecting out from their surface. Approximately 2 km of 0.37 cm square copper magnet wire was precision wound on each shell between the flanges. The shells can be tilted with respect to each other about two orthogonal axes to produce strong magnetic field gradients. This is accomplished by supporting the hemispherical shells on matching sections of spherical bearings mounted on a pair of support cradles. Leadscrews provide the force needed to tilt the massive device. The magnet dissipates 7.5 kw which is removed by water flowing in copper tubes attached to the inside and outside of the shells.

Design goals are a homogeneity of one part in 10^6 for the axial magnetic field when there is no tilt, and a uniform gradient producing a maximum variation of 1½% of the magnetic field at a 5 cm radius for maximum tilt.

Significance: The above described magnet is one of several essential components of a novel NMR imaging system being developed for a variety of diagnostic applications.

Proposed Course: Test field for homogeneity, uniformity of gradients, long-term stability, and repeatability. Make necessary field corrections required to meet design specifications.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10060-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Analytical High Voltage Electron Microscopy and Image Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.D. Leapman	Physicist	BEIB DRS
OTHER:	C.E. Fiori	Physical Scientist	BEIB DRS
	A.F. LeRoy	Chief, Micro. Group	BEIB DRS
	E. Silbergeld	Neurotoxicologist	ETB IRP NINCDS
	J.L. Costa	Staff Physician	CNB NIMH
	K.E. Gorlen	Electronics Engineer	CSL DCRT
	E. Pottala	Electronics Engineer	LAS DCRT
	C.R. Swyt	Physicist	BEIB DRS
	L.K. Barden		CSL DCRT
	J.S. DelPriore		CSL DCRT
	P.S. PLexico		CSL DCRT
	M.A. Douglas		LAS DCRT
	C.C. Gibson	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

Computer Systems Laboratory, DCRT, NIMH, NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The 200 keV Hitachi TEM-STEM electron microscope is now equipped with two microanalytical devices: in electron energy loss spectrometer (EELS) and an energy dispersive X-ray spectrometer (EDX). Both spectrometers have required extensive testing, and significant alterations in the interfacing to the electron-optical column have been necessary. Performance is now substantially improved compared with that after delivery. Such performance will be essential in the biological applications planned in the future. Some preliminary BEIB work has been done on biological and organic samples: the signals or statistics obtained in the spectrum are sufficient for the detection of important elements such as P, N, O and Ca, though the detectability limits have not yet been established precisely. Preliminary data also suggest that energy selective elemental imaging will be achievable using the computer to control the electron probe and to acquire the energy loss signal. Preliminary work has been done with several NIH investigators involving X-ray microanalysis utilizing the improved X-ray performance. Considerably more interaction is planned for the next reporting period.

Interfacing of the PDP 11-60 computer to the microscope is now approximately 20% complete. Much of the hardware has been constructed, such as the high speed medium accuracy and low speed high accuracy digital to analog and analog to digital I/O channels. Three full-time programmers in the computer sciences laboratory have completed the preliminary structure of the operating system.

Objectives: To provide a capability of performing elemental microanalysis on Electron Microscope samples utilizing an Electron Energy Loss spectrometer and a non-dispersive X-ray detector.

Methods Employed: A 200 keV Transmission Electron Microscope with scanning transmission capability is utilized to photoionize microvolumes (containing as small as 10^{-20} grams of matter) of electron microscope specimens. By performing electron spectroscopy on the transmitted electrons and X-ray spectroscopy on the X-rays coming from the photoionized volume of the specimen it is possible to perform elemental microanalysis.

Significance: Electron beam microanalysis permits the solution of certain biological problems which would be difficult, or impossible, by other means.

Proposed Course: To study in detail the problems of applying the technique to biological research and to study in detail the problems involved in this application.

Publications:

Leapman, R.D.: "Extended core edge fine structure in the electron microscope." Proceedings of the 38th Annual Meeting of EMSA, Reno (1980). Baton Rouge, G.W. Bailey (Ed.).

Fiori, C.E., Leapman, R.D., and Gibson, C.C.: "Electrostatic deflection system for use with an electron energy loss spectrometer." Proceedings of the 1980 Meeting of the Microbeam Analysis Society.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10061-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Automated Scanning Electron Beam X-ray Microanalysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.E. Fiori	Physical Scientist	BEIB DRS
OTHER:	A. LeRoy	Chief, Micro. Group	BEIB DRS
	K.E. Gorlen	Electronics Engineer	DCRT
	E. Pottala	Electronics Engineer	DCRT
	D.L. Fry		LEA NHLBI
	C.R. Swyt	Physicist	BEIB DRS

COOPERATING UNITS (if any)

CSL, LAS, DCRT; and LEA, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principal instrumentation for this project, a Cameca MBX 2-50 keV scanning electron beam microprobe, was delivered in January, 1980, and installed during February and March, 1980. The initial performance testing has been accomplished and the machine has been accepted. Some preliminary collaborative biological work is being done and more is planned after modifications are completed to permit the automatic displacement of the sample under the electron beam. More complete automation of the microprobe is being planned and most of the necessary hardware has been ordered. The microprobe will be interfaced to a PDP 11-60 computer. The automation will permit computer control of the specimen stage, electron beam scanning and wavelength dispersive X-ray spectrometers. The bulk of the software will start to be written towards the end of the next reporting period and will require approximately one year to complete.

Objectives: To provide a capability of performing elemental microanalysis on both bulk and thin biological specimens utilizing focussed electron beam induced X-ray spectroscopy.

Methods Employed: A focussed 2-50 keV electron beam is utilized to photoionize microvolumes (containing as small as 10^{-18} grams of matter) of biological specimens. By performing X-ray spectroscopy utilizing Bragg angle X-ray spectrometers, on the X-rays leaving the photoionized volume of the specimen it is possible to perform elemental microanalysis.

Significance: Electron beam microanalysis permits the solution of certain biological problems which would be difficult, or impossible, by other means.

Proposed Course: To apply the technique to biological research and to study in detail the problems involved in this application.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10062-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

IEEE-488 General Purpose Interface Bus Program Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem	Electronic Engineer	EEES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.2	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The ability to produce instrumentation systems using several individual instruments interconnected via the IEEE-488 General Purpose Interface Bus (GPIB) is being developed. With the cooperation of the BEIB-SERP a variety of bus-compatible instruments is being acquired to complement this ability.

Objectives: Develop expertise in the Branch in the use of IEEE-488 GPIB-compatible instruments and controllers. Recommend types of bus-compatible instruments for acquisition by the BEIB-SERP.

Methods Employed: Prototype systems are assembled from equipment available in the rental program and simulation tests run. A system was assembled and set-up in the laboratory of Dr. John Pisano, HE, NHLBI, which digitized and stored the solvent baseline from his liquid chromatograph. This stored baseline was subtracted from the LC output each time a sample was run. The availability of the bus-compatible instruments and controller allowed the quick delivery of a system to confirm the feasibility of the technique and allowed the investigator to be able to take advantage of the data improvement while a dedicated unit was being designed and fabricated.

Significance: The capability of assembling an instrumentation system with a controller and GPIB-controlled instruments allows the EEES to provide a rapid response to an investigators call for instrumentation. By assembling a system with "off-the-shelf" instruments from the SERP, the cost of a special-purpose measurement or control system can be kept quite low. If the experiment is a short-term project the instruments can be returned to the SERP with virtually no expenditures, by the investigator, for equipment.

Proposed Course: Maintain state-of-the-art capability in the field of bus-compatible instruments and controllers. Seek to make this capability better known and understood around NIH.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10063-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Digital Thermistor Thermometer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem	Electronics Engineer	EEES BEIB DRS
OTHER:	R. Berger	Section Chief	LTD NHLBI

COOPERATING UNITS (if any)

LTD, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.1	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

High resolution and high accuracy thermistor thermometers, using microprocessors as control components, are being developed. These units are suitable for process control and data logging uses in the laboratory.

Z01 RS 10063-01 BEI

Objectives: Design and construct a series of high resolution, high accuracy (better than ± 0.01°C) thermometers using precision thermistors as sensing elements and digitizing the results for process control and/or data logging.

Methods Employed: The thermometers are each designed around a microprocessor and high resolution digital-to-analog and analog-to-digital convertors. A known excitation current is applied to the thermistor and the resultant voltage is read. The power level to the thermistor is controlled at a constant value for a minimum of self-heating error. The resistance of the thermistor is calculated and the corresponding temperature is derived from a look-up table which is generated for each thermistor individually.

Significance: These instruments provide high accuracy laboratory thermometers for precision temperature measurements.

Proposed Course: Design additional thermometers with emphasis on different features, i.e., speed, compactness, etc.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 RS 10064-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Indirect Blood Pressure Measurements in Laboratory Animals Using Oscillometry

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.C. Walker	Mechanical Engineer	BEIB DRS
	J.E. Pierce	Chief, LAMSS, OD	NHLBI

COOPERATING UNITS (if any)

NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Currently there are no reliable indirect methods of measuring blood pressure in dogs. Traditional techniques, used in humans, are unsatisfactory primarily because they require the placement of a transducer over the artery being monitored.

Because of the unreliability of traditional techniques we have been investigating a technique called oscillometry. Oscillometry is a method of measuring blood pressure by analyzing the pulse pattern of the cuff pressure oscillations.

In practice, a cuff is placed around a limb and inflated to a pressure above systolic and then slowly deflated. While the cuff is being deflated the amplitude of oscillation in cuff pressure, produced by the arterial pulse beneath the cuff, is monitored. Systolic pressure is indicated by the first significant increase in oscillation amplitude. Diastolic pressure is indicated as the lowest cuff pressure at the point of maximum oscillation in cuff pressure. Currently most investigators using this technique take the point of maximum oscillation to indicate mean arterial pressure.

Objectives: The primary objective of this project is to develop an instrument to indirectly measure peripheral arterial blood pressure in laboratory animals.

Methods Employed: Anesthetized and awake studies were performed on laboratory dogs and pigs. Simultaneous direct arterial and indirect oscillometric cuff pressure measurements were obtained. A laboratory simulation of the oscillatory mechanism has also been employed.

Significance: Animal surgery labs and other laboratories or veterinarian offices could use an indirect device on a daily basis. For various laboratory studies monitoring blood pressure in awake animals is very desirable, particularly with protocols involving atherogenic diets, and drug therapy. Another area of application would be in screening animals for hypertension research. For surgical procedures, an indirect technique will allow blood pressure monitoring before and during induction of anesthesia.

Major Findings: The results of 19 dog experiments and many laboratory simulations indicate that oscillometry measures systolic and diastolic pressures but not the mean arterial pressure (contrary to previous interprelations of the measurement). Future efforts will be directed toward designing an automated oscillometric instrument.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10065-01 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Transient Response of Micro-Calorimeters Using R-C Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.P. Mudd	Biomedical Engineer	BEIB, DRS
OTHER:	R.L. Berger	Section Chief	LTD, NHLBI

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1	1	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The behavior of current microcalorimeters lies between that of true adiabatic or bomb calorimeters and isothermal calorimeters. The location between these extremes depends upon a compromise involving many criteria but most importantly, time constant and sensitivity. The use of an R-C model of the system and Laplace transform techniques will allow us to study the transient behavior of the system to a variety of inputs.

Objective: The objective of the analysis is to determine the input when given the output of the system. Since a micro-calorimeter functionally integrates the signal, the reverse will require, in essence, differentiation and thus will enhance the system noise. Although there are four approaches to this problem that have shown limited success, the FEST (Finite Element Simulation Technique) has yielded the best results to date.

The International Calorimetry Conference has devised a sequence of 7 heat pulses of varying amplitudes and duration to simulate the range of reactions to be encountered in practice. These pulses, termed the Warsaw-Cadarache Pulses, are the input to the model.

Significance: A model has been developed in which the physical system is divided into separate components each of which has a thermal R and C value associated with it. Based on the geometry, these can be determined quite accurately. Thus, the transfer function of each component can be found and when combined will yield the transfer function of the entire system. The results have already been used to redesign the input stage of the calorimeter to reduce loading (thermally), thus resulting in faster rise times or higher a-c sensitivity. The model predictions using the Warsaw-Cadarache Pulses are in the process of being compared to FEST computer results.

Proposed Course: If the results of the comparison with FEST are favorable, this approach will have three advantages: (1) It relies heavily on a known technique for which the mathematics is well documented and relatively simple; (2) it allows the user to evaluate design changes on paper to optimize performance for a given set of operating conditions; and (3) it is (as far as calorimetrists are concerned) inherently less abstract and is an analog of the physical system.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10066-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Egyptian Training Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.P. Mudd	Biomedical Engineer	BEIB DRS
OTHER:	H.W. Metz	Chief	RIS BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Research Instrumentation

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1	PROFESSIONAL: 1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The development of criteria and mechanisms for evaluation of prospective Egyptian engineers for possible training at NIH (RIS) in equipment repair. The final goal is the establishment of repair centers in Egypt for scientific and medical equipment.

Objective: The ultimate objective is the establishment of successful repair centers in Egypt. This will depend upon 3 factors: (1) selection of appropriate repair personnel; (2) proper training of the personnel; and (3) adequate hardware (stock parts, test equipment, etc.). The immediate objective of this project is area 1 and to some extent area 2. We cannot rely on the internal (Egyptian) selection mechanisms because they emphasize too heavily academic or scholastic achievements with very little regard to practical experience or applications.

Significance: A course was developed consisting of 4 weeks of matching lectures and labs. The material was selected to be more advanced than that in two preceding courses (NRC I and NRC II) presented by USAID. This new course had two primary goals: (1) to evaluate candidates for possible future training at NIH and (2) to provide a practically oriented, more advanced course to follow NRC I and II.

To achieve these goals, the course was divided into two parts. The first covered the use of linear and non-linear integrated circuits while the second covered their application involving transducers.

In the first part, the emphasis was on the practical limitations of integrated circuits. This was intended to bring all of the students up to an equal level to allow a more meaningful aptitude evaluation in the second part.

The second part involved using the basic circuits of part one to form signal processing blocks to convert transducer signals into useable and appropriate outputs. Here, the emphasis was on practical design which involves making intelligent compromises concerning signal to noise ratio, bandwidth, gain, etc.

Proposed Course: The course is tentatively planned for presentation November-December 1980. Previous versions were presented in the Summers of 1978 and 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10067-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Review and Integration of Micro-Calorimeter System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C.P. Mudd	Biomedical Engineer	MES BEIB DRS
OTHER:	R.L. Berger	Section Chief	LTD NHLBI
	W.S. Friauf	Electrical Engineer	EEES BEIB DRS
	C. Gibson	Electrical Engineer	EEES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Electrical and Electronics Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1	PROFESSIONAL: 1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

For the past several years, considerable time and effort have been expended on the various aspects of a micro-calorimetry system. Due to the complexity and interdisciplinary nature of the work, the first model did not perform to expectations. Several problem areas were identified and led to subsequent projects (e.g. 71-78-167E, Monolithic Thermopile Design and 71-80-144M, R-C Analysis of Micro-Calorimetric Transient Response). The review and redesign led to the achievement of heat resolution of 300n watts and long-term stability of ± 200nw (rms). A list of performance criteria for a differential calorimeter has been developed and the new sensor design is being evaluated in a new calorimeter.

Objective: The objective for the microcalorimeter is to reduce all noise contributions to approximately the same magnitude. In this case, the ultimate limitation on resolution and drift is determined by the electronics (300n watts and ± 200n watts (rms)/24 hours respectively in terms of the measurement). The low long-term stability is desirable for proposed metabolic studies involving cancer cells and the high resolution is desirable for adequately determining enzyme kinetics.

Significance: To date, we have produced one differential batch micro-calorimeter which meets the above specifications. To achieve this, we identified and eliminated the following problems:

(1) A "motion artifact" which occurred when the rotor was inverted to mix the reagents. The cause was two-fold: bearing heat from mis-aligned bearing supporting the rotor and mixing of air within the constant temperature chamber which in effect produced an impulse response from the temperature control circuit. To reduce the temperature gradient within the chamber, special heaters were designed to give a uniform heating density (watts/cm^2) over the surface.

(2) A drift linked to room temperature was identified and reduced by adding a second control on the outside of the calorimeter to hold the temperature constant ± 0.2°F.

(3) New sensors were purchased which increased the sensitivity by a factor of 3. From a model of the system, we were able to redesign the input stage (mechanical) so that the rise time remained unchanged.

Proposed Course: We are currently in the process of building a complete calorimeter system for an investigator at NIH. The system will be built by a private contractor and we will evaluate its performance after construction.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10068-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Rat Vocalization Analysis System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	James L. Hill	Visiting Associate	LBEB NIMH
OTHER:	John B. Calhoun	Research Psychologist	LBEB NIMH
	W.J. Vaughn	System Programmer	STD NIMH
	Horace E. Cascio	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

Laboratory of Brain Evolution and Behavior

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.9	PROFESSIONAL: 0.8	OTHER: 0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Vocal communication among members of free ranging population of rats housed in a complex laboratory. Enclosures are either audible or are ultrasonic. Ultrasonic vocalizations tend to be more prolonged and to form patterned sequences. Rats vocalizing simultaneously are capable of utilizing separate frequency bands so that each vocalization signal can be distinguished. Rats required to perform cooperatively appear to exhibit different and, possibly more complex vocalization patterns, than those rats with free access to food and water resources.

Objectives: To design and install a system to investigate whether the quality, quantity and pattern of rat vocalization change when the animals are required to perform complex cooperative behaviors to meet their physiological needs.

Methods Employed: A recording system was designed using a special microphone and amplifier which has a frequency range (20 Hz - 200 KHz) to pick up the audible and ultrasonic vocalizations. The microphone was mounted in a parabolic reflector to increase directivity. The vocalization signal is coupled to a Tektronic 5L4N Spectrum Analyzer and the video output of the 5L4N is applied to a PDP11/04 computer. Electronic interfacing circuitry was required for the video signal and also to provide a start pulse to synchronise the 5L4N to the computer. Software within the computer then classified the vocalizations according to type and frequency. Graphics output is of two major types: (1) the trace of the power curve and (2) a representation of each vocalization as a vertical line spanning the frequency band. To aid in the determination of the type of vocalizations that are associated with specific behaviors, an intercom system was installed so that a direct observation could be made with the computer recording. This vocal-ethogram will provide the base line for comparison of experimentally induced changes in vocalization on behavior.

Major Findings: Most of the sounds are ultrasonic vocalizations. Sounds were distinguishable as to squeaks, when rats move through the environment and to conversations between rats. At present the investigation is continuing to correlate the occurrence of these and other patterns of vocalizations with visual observations of social behavior and computer records of movement patterns.

Proposed Course: To provide additional instrumentation as required to study the comparison of the vocalizations of rats required to perform cooperative behaviors with those of rats that can satisfy their needs *ad lib*, and to add a comparison of the vocalizations of neopalliectomized rats to those of normal rats to determine the contribution of the neocortex to the regulation of the type and patterning of vocalizations.

Significance: Vocal communication, which plays a major role in mammalian social behavior, may become changed as an outward manifestation of stress or some altered brain function. An animal model, is being presented, that is being used (1) to discover how long-term stress influences vocal communication and (2) to investigate the role of the neocortex in the regulation of vocal communication. Furthermore, the extremely complex and prolonged patterns of vocal communications between rats suggest that Norway rats, *Rattus norwegicus*, may lead to the use of this species as an animal model for the study of the early evolution of communication that culminated in human language.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10069-01 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Two Automated Test Sets Mod. III for Checking Safety of Biomedical Equipment

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Wooten	Electronics Engineer	EEES BEIB DRS
OTHER:	H. Cascio	Electronics Engineer	EEES BEIB DRS
	W. Friauf	Section Chief	EEES BEIB DRS
	R. Corsey	Electronics Engineer	ACES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronics Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These safety test units are designed to provide accurate measurements of the ground resistance and current leakage of equipment located in the Clinical Center. Two test sets have already been in operation for 7 years. These new units will perform the same tests, but they have been updated to provide automated data acquisition and storage.

Objectives: The objective is to provide an automated test set which can safely and accurately measure the parameters of devices in their operating environment. Also, the objective is to facilitate the handling and storage of this data, so that the safety of the equipment being tested can be better evaluated and statistical and trend analysis of past and present data can be done.

Methods Employed: Using microprocessor technology, manual input and bar code scanner input can be interfaced to the test set to provide identification of the equipment and annotations on the test itself. The data is output to cassette tapes which are compatible with the IBM/360 or DEC 10 computer. A program is being written to input the data and file it for better documentation and analysis for the user.

Significance: By monitoring the results from the safety test data, problems in the safety and every day operation of the equipment can be detected or even predicted to prevent hazards to the patients.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10070-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Conceptual Adaptation and Evolution

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.B. Calhoun	Research Psychologist	LBEB NIMH
OTHER:	R.W. Ridez	Research Psychologist	LBEB NIMH
	G.A. Bagley	Computer Programmer	LBEB NIMH
	H.E. Cascio	Electronics Engineer	BEIB DRS
	A.H. Rich	Mechanical Engineer	BEIB DRS
	D.R. Ahuja	Research Fellow	SPH HU
	R.A. Newell	Electronic Engineer	STD NIMH

COOPERATING UNITS (if any)

Laboratory of Brain Evolution and Behavior

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronics Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 3.4	PROFESSIONAL: 1.2	OTHER: 2.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Hybrid rats, Rattus norwegicus, are used to investigate a model of nongenetic adaptation with rats living in a stable environment under crowded conditions. A control population received food and water under normal conditions with no demands for learning cooperative tasks placed upon them. Rats maintained at twice normal population density obtained food and water resources by learning cooperative tasks. Results indicate that these latter rats show: (1) reduced intensity of fighting, (2) increasing maintenance of body weight, and (3) development of modes of reproductive control, including killing of young. We conclude that acquisition of cooperative behavior reduces crowding related stress.

Objectives: To design and fabricate testing apparatus to enable the determination of the effects of an investigator-induced acquisition of cooperative behaviors by rats living at twice optimum density in contrast to a control population without the opportunity to acquire cooperative behaviors.

Methods Employed: A controlled drinking device was fabricated that can be switched to a cooperative drinking mode which required that one rat must be present in each of two adjacent units for either one to obtain water. In addition to their normal sources of food and water, three different reward situations were provided, each with a different reward. First, a drinking device which gives saccharine water; secondly, a sunflower seed dispenser, and thirdly, a swing rod which has an orange quarter placed at the bottom of the rod. The above apparatuses can be altered after a period of time to deman cooperative behavior in order to obtain rewards. A computer data acquisition system continuously monitors movements between habitat compartments and response to food and water acquisition apparatuses by identity of each rat.

Major Findings: The COOP experimental subjects, in contrast to the DISOP controls, exhibit: (1) less intense fighting with fewer wounds received, (2) sustained greater body weight, (3) decreased conception, and (4) increased killing of recently weaned young by adult females. These results acquire meaning when viewed against a finding of a difference in the distribution of "social power," the ability to engage in, and to exercise dominance during social encounters.

Proposed Course: Continue to provide technical support to this project until its conclusion.

Significance: Humans are exposed to environments which are increasingly becoming more variable, complex, and changing. The current rate of change introduces undesirable stress on individuals and produces broader instabilities in society. The research with rats suggest more cooperative social roles can ameliorate stressful consequences of physical and social environmental change. However, introduction of cooperative social roles produce instabilities in social relationships which last longer than does the learning of the new cooperative manners of behaving.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10071-01 BEI

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes for Cardiac Instrumentation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Chief	MES BEIB DRS
OTHER:	R. Patterson	Senior Investigator	NHLBI
	J.I. Peterson	Chemist	ChES BEIB DRS

COOPERATING UNITS (if any)

Cardiology Branch, NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical and Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: .8	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The use of miniature fiber optic probes for acute insertion into canine myocardium is being investigated. Measurements of pH, local blood flow and local capillary permeability in the presence of various interventions is contemplated. Practical problems dealing with insertion into tissue, validation of readings, elimination of motion artefacts, and overall characterization of in-vivo performance are of major interest. Preliminary results are encouraging.

Objectives: Perfect and enhance previously developed techniques (described in last years report) utilizing miniature fiber optic probes to measure pH, tissue perfusion and capillary permeability in canine hearts in vivo.

Methods Employed: Utilize existing miniature fiber optic probes to perform measurements in acute dog experiments. Perform tests to determine practical problems, e.g., breakage, tissue insertion, artefacts, calibration difficulties, elimination of motion artefacts, zero shifts, hysteresis, etc. Develop solutions to above problems using improved probes and signal processing instrumentation.

Significance: At present there are no completely satisfactory techniques for measuring local pH, perfusion, and capillary permeability in-vivo in an "on-line" manner. Perfection of these measurements would represent a great advance in the techniques presently available to experimental cardiologists and other biomedical researchers not only in terms of convenience, but also in terms of opening up many new areas of investigation.

Major Findings and Proposed Course: On the basis of preliminary experiments it appears that:

(a) pH measurements behave in a qualitatively correct manner but difficulties still remain with inserting the 0.3 mm diameter probe without traumatizing the local region when using in the beating heart; validation of probe accuracy must be performed. A second generation multi-channel input interfaced with a Tektronix 4052 calculator will be built.

(b) Perfusion measurements are feasible, i.e., there is acceptable signal-to-noise ratio. Motion artefacts must be eliminated and an approach is being investigated. Validation using microspheres will be performed once an automatic gain ranging system is implemented so that traces can be reliably obtained. Various flow limited fluorescent markers in addition to fluorescein will be sought.

(c) Capillary permeability studies will be investigated after the perfusion and pH techniques have been perfected. Fluorescent labeled compounds of appropriate molecular weight (possibly fluorescein labeled albumin) will be sought and used.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10072-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Clinical Evaluation of Membrane Oxygen Dissociation Curve Analyser

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	L. Thibault	Mechanical Engineer	ACES BEIB DRS
	H. Tipton	Mechanical Engineer	ACES BEIB DRS
	D. Lees	Staff Anesthesia	CC NIH

COOPERATING UNITS (if any)

CC - NIH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 2	PROFESSIONAL: 1.5	OTHER: .5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A fully automated, computer controlled method for determining and plotting the entire hemoglobin-oxygen dissociation curve on less than .5 cc of blood has been developed and is being introduced to clinical practice. A micro-computer controls the calibration of the system as well as the initial desaturation and subsequent saturation of the blood specimen.

Methods Employed: Initially the specimen is desaturated by exposure to a CO_2/N_2 mixture. Once the pO_2 falls below 0.5 torr, the computer automatically starts the saturation with a mixture of oxygen and CO_2. Gas is exchanged with the sample in a reaction cell across a silicone rubber membrane which mechanically separates the two phases. The sample solution is contained within an annular region formed by the cylindrical membrane and the sample cavity walls where it is stirred by a thin-walled cupshaped stirrer, magnetically coupled to an outside motor-driven rotor. A conventional polarographic oxygen electrode continuously monitors the partial pressure of oxygen in the sample. The amount of oxygen delivered to the sample is calculated by integrating the diffusion equation and the measured pO_2 gradient across the thin silicone membrane.

Major Findings: The described system appears to be a simple and reliable way of obtaining the hemoglobin-oxygen dissociation curve for clinical applications.

Publications:

Thibault, L.E., Kusnetz, R., Winslow, R.M. and Berger, R.L.: An instrument to determine the hemoglobin-oxygen equilibrium curve based on an analytical model for the transport of oxygen across a semi-permeable membrane. Advances in Bioengineering, American Society of Mechanical Engineers, New York, 1978, pp. 107-108.

Thibault, L.E., Schuette, W.H., and Lees, D.E.: An instrument to determine the hemoglobin-oxygen equilibrium curve based on the calculated diffusion of oxygen across a semi-permeable membrane. Medical and Biological Engineering and Computing Journal of the International Federation for Medical and Biological Engineering (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10073-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Secondary Emission Experimental Mass Spectrometer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Associate	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principal instrumentation for this project, the SIMS-quadrupole mass spectrometer, PE-270 double-focusing mass spectrometer, electron and ion guns will not be delivered until the next reporting period. The major effort on this project to date has been in the evaluation of the literature on the related subjects to the proposed instrument: secondary ion mass spectrometry, surface ionization, secondary ion and electron emission, cold emitters; establishment of specifications of the instrument. The SIMS mass spectrometer chosen is an Extranuclear "plus" SIMS secondary ion mass spectrometer, the double-focusing mass spectrometer model PE-270 to be transferred to NIH from the Argonne Res. Labs, electron gun EFG-7J and power supply EGPS-7J will be purchased from Kimball Physics Inc.; the ionization chamber has been ordered from MDC Manufacturing Co., and will consist of a stainless steel beel-jar with four 6" and four 2.75" CF flanges and two 8" flanges; the vacuum system Balzers TSH-511 will be incorporated to evacuate the ionization chamber.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10074-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Study of analytical applications of QUISTOR

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Associate	BEIB DRS
OTHER:	S. Markey	Chemist	LCS NIMH

COOPERATING UNITS (if any)

LCS NIMH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The quadrupole ion store (QUISTOR) or three dimensional ion trap has received little attention among analytical chemists compared to the quadrupole mass filter or two dimensional quadrupole. This is in part due to the fact that QUISTOR primarily has been developed, studied, and used by physicists as partial and total pressure analysers and residual gas analysers and most recently as electronically controlled ion-molecule reaction chambers. Recent works by G. Lawson, R.F. Bonner and R. March employing a three dimensional quadrupole ion trap as an ion source for a mass spectrometer has opened new avenues for the QUISTOR as an analytical tool. The QUISTOR is expected to be more compact, the resolution of the instrument would not be mass dependent as for quadrupoles, and the sensitivity of the device, specifically when detecting single ions, may be improved compared to a quadrupole mass spectrometer combined with a conventional ion source.

The Quadrupole Ion Store was constructed and machined from stainless steel, specifications for the driving electronics have been established, RF-generator modified by Exranuclear Labs. will be used to power the QUISTOR, pulse electronics will consist of a Boxcar Averager and Gated Integrater by EG&G, two pulse generators by HP, X-Y Recorder and Tektronix Oscilloscope.

Objectives: To develop a QUISTOR-mass spectrometer combination and to study the possible applications in analytical mass spectrometry.

Methods Employed: A three dimensional quadrupole electric field will be used to store ions of interest. This field will be formed by three electrodes of a hyperbolic geometry made of stainless steel, which will consist of two "endcaps" and one central ring. The electron gun will be used to ionize molecules of compounds to be studied. The RF-electric field will be applied to a ring electrode and creation and ejection pulses to the end-caps.

Significance: Development of a three-dimensional ion store and its application in mass spectrometry may result in improvements of detection capabilities of existent instruments and may increase limits of detection of compounds of biological interest.

Proposed Course: Construct the driving electronics and detection system for the QUISTOR. Test the device and study its storage capabilities. Interface the quadrupole ion trap with the gas inlet sysem and the gas chromatograph. Employ different types of electron emitters: hot filaments, field emitters, cold cathodes and find the most suitable emitter for the proposed device. Study the applicability of the QUISTOR to mass spectrometric analysis of drugs and other compounds of biological interest.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10075-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of a new method for resolving power measurement

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Associate	BEIB DRS
OTHER:	D. Rosenthal	Senior Chemist	CLSG RTI

COOPERATING UNITS (if any)

Chemistry and Life Sciences Group, Research Triangle Institute

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ [✓ (c)] NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Decachlorobiphenyl and decabromobiphenyl have been analyzed under positive and negative ion chemical ionization and positive ion electron impact conditions for the purpose of using these compounds as references to evaluate the resolving power of mass spectrometers in a wide mass range (M/Z 100-1000). Molecular clusters and some fragments have been detected with different types of mass spectrometers: magnetic sector as well as quadrupoles, including A.E.I. MS-9, LKB-9000, LKB-2091, Finnigan 3200 and Finnigan 4000. The criteria to determine the resolving power have been found based on the measurement of the minima of two adjacent peaks of the molecular cluster of DCB or DBB. Molecular clusters for DCB and DBB were determined theoretically by plotting the individual ions which constitute each profile at the desired resolution using a standard Gaussian distribution of intensities, and then summing the individual ions with the weighting factors derived from the theoretical statistical isotope distribution ratios of carbon, chlorine, and bromine. By comparing the theoretical values of minima vs. resolution with the experimentally found values of minima between the same two adjacent peaks, the resolving power of a given mass spectrometer can be determined. The method developed here and the reference compounds DCB and DBB will be recommended to manufacturers and users of mass spectrometers as an easy and accurate way to estimate the resolving power of their instruments both for instrument acceptance and as a routine check-out.

Objectives: To develop a method to measure the resolving power of various types of low resolution mass spectrometers which will be easier, faster and require less effort than the conventional methods.

Methods Employed: Theoretical values of ion abundances for molecular clusters of decachlorobiphenyl and decabromobiphenyl will be used to determine the resolving power of mass spectrometers by comparing them with the experimental values of minima between two adjacent peaks in the molecular cluster.

Major Findings: The calibration curves MIN=f(R) have been found for molecular clusters of DCB(M/Z 498) and DBB(M/Z 944). The comparison between the theoretically derived MIN values and the experimental data show good agreement between observed and calculated values in the resolution range of 150-500 for DCB and 300-900 for DBB. Thus the two compounds cover the useful range of a low resolution mass spectrometer, i.e., 150-900. It also has been found that DBB may be used as a sensitivity test reference for quadrupole mass spectrometers in a high mass range (600-1000). It can be done by comparing intensities of the peaks centered at M/Z 944 and M/Z 784. Their ratio should be about 0.5.

Significance: A simple method to determine the resolving power of mass spectrometers has been developed. The method can be used in all types of mass spectrometers and with different ionization techniques (electron impact, chemical ionization, positive or negative ions, etc.). The method will be beneficialy to all mass spectrometry users and may improve the specifications of the instruments at their acceptance.

Proposed Course: The experimental data for the measurement of the resolving power on different types of mass spectrometers will be analyzed. The inlet system to conveniently introduce DCB and DBB into the ion source region of the mass spectrometers will be developed. The possible automation of the procedure with the help of a dedicated computer system (MS/DS) will be evaluated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10076-01 BEI

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Elemental Analysis of Microdroplets

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.F. LeRoy	Chief, Micro. Group	BEIB DRS
OTHER:	N. Roinel	Chemist	CEN, France

COOPERATING UNITS (if any)

Department of Biology, Centre d"Etudes Nucleaires, Saclay, France

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c)X NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principal instruments used in this project are the Cameca MBX 2-50 KeV scanning electron beam microprobe and a Cameca MS-46 electron microprobe, each equipped with two wavelength dispersive spectrometers. Quantitative elemental analysis in volumes of the order of 10^{-10} liter are possible using these instruments. The signal for some elements changes with time as a function of beam current density, sample mass thickness and some other characteristics of the samples. A systematic quantitative study of the variables that affect stability of the signal has been undertaken to establish the ranges of values of these variables that permit usable results to be obtained.

Objectives: To establish the ranges of instrument operating conditions that yield stable signals for the elements analyzed with the MBX microprobe.

Methods Employed: Mathematical analysis of data obtained on representative microdroplets to quantify dependence of element X-ray signal on operating conditions as a function of time.

Significance: To provide a sound basis for quantitative analysis of microdroplets.

Proposed Course: To extend the number of variables included in the study to include temperature of the sample analyzed and the sizes of crystals analyzed.

Publications:

Roinel, N.G. and LeRoy, A.F.: Variations in characteristic signals of the elements during microprobe analysis of droplets: A review. Microbeam Analysis, 129-132, 1980.

LeRoy, Andre and Roinel, Nicole: Quantitative analysis of lyophilized solutions: Loss of elements during the irradiation time as a function of sample current density and mass thickness. Proceedings of the Seventh European Congress on Electron Microscopy, The Hague, The Netherlands, August, 1980.

NIH Library, Building 10
National Institutes of Health
Bethesda, Md. 20205

DATE DUE

GAYLORD
PRINTED IN U.S.A.

NIH LIBRARY
Amazing Research.
Amazing Help.
http://nihlibrary.nih.gov

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

NIH LIBRARY
4 0142 3331

NIH LIBRARY
3 1496 00179 4851